REMARKS

Statement of the Substance of the Interview:

The undersigned notes with appreciation the personal interview granted by Examiners Borgeest and Kemmerer on March 28, 2006. The Examiner's Interview Summary accurately describes the substance of the interview. The items discussed are addressed in this reply.

Specification Amendments:

The specification has been amended to correct a typographical error. It is clear from the specification, for example, at page 9, Table I, that Cetrorelix, ANTRARELIX®, Antide, and Ramorelix are GnRH antagonists, not agonists. The amended paragraph had been previously amended to capitalize trademarked names.

No new matter has been entered by this amendment. The Examiner is hereby requested to enter this amendment.

Claim Amendments:

Claims 14 has been amended to recite that the claimed invention is drawn to a method for decreasing cellular replication of a GnRH-receptor positive tumor selected from the group consisting of a tumor originating in one or more of the brain, nervous system or meninges of the brain; Ewing sarcoma; Kaposi sarcoma; and malignant melanoma, said method comprising administering to a subject a replication decreasing amount of one or more of a GnRH agonistic analogue or a GnRH antagonistic analogue, so as to decrease cellular replication of the GnRH-receptor positive tumor. Support for the amendment may be found, for example, at page 24, Table II in the as-filed specification where GnRH-receptor positive tumors (including glioblastoma multiforme (GBM), glioma, meningeoma, and chordoma) are described, at page 14, line 26 to page 15, line 4 where Kaposi sarcoma, malignant melanoma and Ewing sarcoma are described, and at page 25, line 15 to page 26, line 13 where inhibition of tumor cell proliferation by a GnRH agonistic analogue (Triptorelin) or a GnRH antagonistic analogue (Antide) is

described. Claim 15 has been amended to recite that the claimed invention is drawn to the method of claim 14 wherein the GnRH-receptor positive tumor is Kaposi sarcoma. Claim 16 has been amended to recite that the claimed invention is drawn to the method of claim 14 wherein the GnRH-receptor positive tumor is Glioblastoma multiforme, medulloblastoma, pinealoma, neuroblastoma, craniopharyngeoma, meningeoma, chordoma, Ewing sarcoma, malignant melanoma, or Kaposi sarcoma. New claim 18 is drawn to the method of claim 14 wherein the GnRH-receptor positive tumor is malignant melanoma. Applicant specifically reserves the right to file appropriate continuing and/or divisional application(s) drawn to any subject matter withdrawn by these amendments.

New claim 19 is drawn to a method for decreasing cellular replication of a GnRH-receptor positive tumor selected from the group consisting of a tumor originating in one or more of the brain, nervous system or meninges of the brain; Ewing sarcoma; Kaposi sarcoma; and malignant melanoma, said method comprising administering to a subject a replication decreasing amount of a GnRH agonist or GnRH antagonist coupled to a cytotoxic substance, said GnRH agonist or GnRH antagonist being a GnRH analogue, so as to decrease cellular replication of the GnRH-receptor positive tumor. New claim 20 is drawn to the method of claim 19 wherein the GnRH-receptor positive tumor is malignant melanoma. Support for these claims may be found, for example, at page 10, lines 21-22, of the as-filed specification, where a GnRH agonist or antagonist (ligand) coupled to a cytotoxic agent is described, and at page 8, lines 12-14, where tumor therapy using GnRH agonists and/or GnRH antagonists or conjugates is described.

No new matter has been entered by these amendments. The Examiner is hereby requested to enter these amendments.

Copies of References:

In response to the April 4, 2006 Office Action, Applicant provides herewith copies of the following references which were included in the information disclosure statement filed August 17, 2005:

1. He et al., 1986, Clinical Chemistry, Col. 32, No. 6, pp.1159, abstract #542.

2. Hoitink et al., Stability of Gonadorelin and Relation Compounds, dissertation, U. of Ultrecht, 8/6/1998, CH. 1, p. 15.
3. Rote Liste, 1997, reference No. 50 040-56 .

The Examiner is invited to contact the undersigned should further information be needed.

Rejection under 35 U.S.C. §112:

The Examiner's rejection of claims 14-17 as allegedly failing to comply with the enablement requirement is respectfully traversed in view of the amendments of the these claims. The Examiner asserts that Applicant has not provided guidance to indicate that GnRH receptors are present in all of the cancers that Applicant's methods are intended to treat. As amended, independent claims 14-16 are drawn to methods for decreasing cellular replication of GnRH-receptor positive tumors using GnRH agonistic or antagonistic analogues. Support for the amendment may be found in the as-filed specification. For example, Table II, at page 24, shows that tumors originating in the brain, nervous system or meginges of the brain, including glioblastoma multiforme (GBM), glioma, meningeoma and chordoma, are GnRH-receptor positive. Example 14 at page 25, line 1 to page 26, line 13 of the specification describes inhibition of melanoma cell proliferation by a GnRH agonist (Triptorelin) or a GnRH antagonist (Antide), providing support for the presence of GnRH receptors on human malignant melanoma. Support for the presence of GnRH receptors on Kaposi sarcoma may be found, for example, at page 6, lines 6-7 of the specification. Further evidence of the presence of GnRH-receptors in melanoma or Kaposi sarcoma has been provided in related U.S. Application Serial No. 10/327,621 in the form of a declaration executed by the inventor, Dr. Johannes C. van Groeninghen, according to 37 C.F.R. § 1.132 (copy provided herewith). Additionally, Moretti et al., J. Clin. Endocrino. Metab., 2002, 87(8):3791-7 (copy provided) showed that GnRH receptors are present in melanoma cells. Yeung et al., Mol. Human Reproduction, 2005, 11(11): 837 (abstract only; copy provided), reported that GnRH receptors are present in a human cerebellar medulloblastoma cell line.

The Examiner also contends that the specification provides only three *in vitro* experiments indicating inhibition of proliferation and these *in vitro* data are not predictive of anti-cancer activity. With respect to 35 U.S.C. §112, first paragraph-enablement of chemical/biotechnical applications, the USPTO has made it clear that an *in vitro* or *in vivo* animal model example in the specification constitutes a "working example" if that example correlates with a disclosed or claimed method invention, and a rigorous or an invariable exact correlation is not required. M.P.E.P. 2164.02, citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). A string of references, both before and after the filing date of the present application, show that *in vitro* inhibition of cell proliferation by a GnRH agonist or antagonist correlates with *in vivo* anti-cancer activity:

(1) In Pinski et al., Int. J. Cancer., 1994, 59(1): 51 (abstract only; copy provided), it was shown that a LHRH (also referred to as GnRH) antagonistic analogue and a LHRH agonistic analogue not only significantly prolonged the mean survival time of rats bearing prostatic adenocarcinoma, but also suppressed proliferation in cell cultures, respectively. Human clinical evidence that treatment with a LHRH agonist led to reduction of prostate tumor mass and metastases may be found in Damyanov et al., Eur. Urol., 2001, 40(4):474-6 (abstract only; copy provided).

(2) Kim et al., Gynecol. Oncol., 1999, 74(2): 170-180 (abstract only; copy provided), showed that continuous exposure of two human ovarian cancer cell lines and xenografts to a GnRH agonist resulted in growth inhibition of cancer cells in a dose- and time-dependent manner. A phase II clinical study of showed that Cetrorelix, a GnRH antagonist, has activity against ovarian cancer in human patients. See Verschraegen et al., 2003, 90(3):552-559 (abstract only; copy provided).

(3) In Vincze et al., J. Cancer Res. Clin. Oncol., 1994, 120(10): 578 (abstract only; copy provided), a GnRH antagonistic analogue (MI-1544) induced a significant decrease in cell numbers of human breast cancer cell lines in vitro, and inhibited the growth of xenografts in vivo. Further evidence of in vivo antiproliferative effect of a GnRH agonist and a GnRH antagonist on breast cancer may be found in Yano et al., Breast Cancer Res. Treat., 1992,

21(1):35-45 (abstract only; copy provided), in which tumor volume was significantly suppressed by both the GnRH agonist and the GnRH antagonist in nude mice. Clinical studies indicate that goserelin, a GnRH agonist, is effective for chemotherapy for early breast cancer. See Kaufmann et al., Eur. J. Cancer, 2003, 39(12):1711-7 (abstract only; copy provided).

(4) Limonta et al., Frontiers in Neuroendocrinology, 2003, 24: 279-295 (page 287). (previously provided with the response filed on 08/17/2005), reported inhibition of melanoma cell proliferation both in vitro and in vivo by GnRH agonists.

Taken together, these studies demonstrate there is correlation between *in vitro* inhibition of proliferation and *in vivo* suppression of tumor growth by GnRH antagonistic analogues or GnRH agonistic analogues. Therefore, the *in vitro* experiments in the specification constitutes a "working example" which would enable one skilled in the art to practice the claimed invention.

The Examiner contends "the growth inhibitory activity for a single cell line is not very informative" citing Shi et al., which analyzed the test results of 70,000 compounds against 60 cancer cell lines in the NCI Anticancer Drug Discovery Program. The GnRH agonistic and antagonistic analogues in the claimed invention are distinct from the compounds screened in the NCI Anticancer Drug Discovery Program. The GnRH analogues are well-studied compounds and their mechanism of action is known, namely by binding to the GnRH receptor and affecting downstream biological events such as signal transduction. Much less is known about each of the 70,000 compounds screened in the NCI program, which include synthetic compounds and a large number of natural product extracts compounds. Thus, unlike the compounds tested in the NCI program, the growth inhibitory activity of the GnRH analogues for a single cell line can be informative. Furthermore, Shi et al. also report "the growth inhibitory activity for a single cell line is not very informative, but we have found that activity patterns across the 60 lines provide incisive information on the mechanisms of action of screened compounds. . . Similarity in activity patterns very often indicates a similarity in the mechanism of action." GnRH agonistic or antagonistic analogues have been tested in a variety of cancer cell lines, including melanoma, breast cancer, ovarian cancer, and prostatic adenocarcinoma, as shown in the references cited in the proceeding paragraphs. The similarity in the tumor inhibitory activity observed in the *in*

vitro experiments in the specification, and in the *in vitro* and *in vivo* experiments in the literature, indicates a similarity in the mechanism of action. Thus the *in vitro* experiments in the specification provide sufficient guidance for one skilled in the art to practice the claimed invention

The Examiner further points out that the prior art is silent with regard to GnRH agonist treatment of the diseases listed in claims 14-16. That is appropriately so because the claimed invention is novel and patentable. On the other hand, there is a significant amount of literature describing the use of GnRH agonist or antagonists in treatment of other types of cancers in *in vivo* models. For example, the references cited in the proceeding paragraphs, including Pinski et al. (Int. J. Cancer., 1994, 59(1): 51-5), Yano et al. (Breast Cancer Res. Treat., 1992, 21(1):35-45), and Kim et al. (Gynecol. Oncol., 1999, 74(2): 170-180), all described *in vivo* treatment of tumors with GnRH agonists. Thus, the art provides sufficient guidance for one skilled in the art to apply the claimed invention to the tumors listed in the claims.

The Examiner further contends that "the claims encompass all GnRH agonists (as well as antagonists), including those not yet known in the art", and "because of the complex nature of all of these factors, it is not predictable which agonists would function as claimed." Although Applicant does not agree that any of the claims lack compliance with the enablement requirement, to expedite prosecution, independent claims 14-16 have been amended to recite that the GnRH agonist or antagonist is a GnRH analogue. In *Amgen, Inc. v. Chugai Pharmaceutical*, it was held that one may define a compound by "whatever characteristics sufficiently distinguish it." 927 F. 2d 1200, 1206, 18 U.S.P.Q.2d 1016, 1021 (Fed. Cir. 1991). *In re Herschler* found sufficient "a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description." M.P.E.P. § 2163, II.A.3.(a), citing *In re Herschler*, 591 F.2d 693, 697, 200 U.S.P.Q. 711, 714 (CCPA 1979). One of ordinary skill in the art knows the well-defined common structural features of the GnRH peptide. A peptide analogue of GnRH would also have these common structural features and therefore be easily identifiable as a GnRH analogue without undue experimentation. Such

analogues include well-known compounds such as leuprorelin, buserelin, goserelin, antide, ramorelix, cetrorelix, etc (see Table I at page 9 in specification). The agonist activity of GnRH analogues is well-known in the art to be attributed to such structural features as the [R]-amino acid replacement at the 6^{th} position together with aza-amino acid replacement at the 10^{th} position or substitution of the Gly^{10}-NH2 residue by an ethylamide group in the parent GnRH molecule. (See, e.g., Hoitink, M., *Stability of Gonadorelin and Related Compounds*, dissertation, University of Utrecht, June 8, 1998, Chapter 1, page 15.) These modifications render the GnRH agonistic analogs 100-200 times more potent than the parent peptide GnRH. (*Id.*). Likewise, most GnRH antagonistic analogues were obtained either by eliminating the His^2 residue or its side chain at the second position in the GnRH peptide, in combination with replacement of 5-8 of the original amino acids by unnatural amino acids (*Id.*). Other GnRH analogues may be readily characterized as agonists or antagonists by methods readily known and available to those of ordinary skill in the art. Thus, the claims, as amended, recite not only functional features, but also functional features directly related to structural features known to one of ordinary skill in the art. Therefore, undue experimentation would not be required for the skilled artisan to use the claimed invention.

For the reasons set forth above, Applicant submits that the claims of this application meet the requirements of 35 U.S.C. §112. Withdrawal of the rejection is requested.

Double Patenting:

The Examiner's provisional rejection of claims 14-17 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9, 10, 12 and 13-18 of co-pending U.S. Application Serial No. 10/327,621 is respectfully traversed. The M.P.E.P. states "if a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." M.P.E.P. 804.I.B.1. Because co-pending U.S. Application Serial No. 10/327,621 is later-filed and is

rejected on other grounds, the Examiner should withdraw the double patenting rejection and allow the present application to issue.

Withdrawal of the rejection is requested.

Conclusions:

For the reasons set forth above, Applicant submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims of this application at an early date is earnestly solicited.

Enclosed is a $60.00 check for the Petition for Extension of Time fee. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: August 4, 2006

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